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10/500,173	06/24/2004	Katsuhito Takahashi	4439-4022	3299

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EXAMINER	
POPA, ILEANA	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,173	TAKAHASHI ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-13,18 and 20-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6-13,18 and 20-36* is/are rejected.

7)☒ Claim(s) *27 and 29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/23/2007 has been entered.

2. Claims 2, 5, 14-17, and 19 have been cancelled. Claims 1, 3, 4, 6-13, 18, 20-23, 26, and 29-36 have been amended.

Claims 1, 3, 4, 6-13, 18, and 20-36 are pending and under examination.

3. The rejections of claim 5 on the ground of nonstatutory obviousness-type double patenting, under 35 U.S.C. 112 for not complying with the enablement requirement, under 35 U.S.C. 103(a) as being unpatentable over Martuza (U.S. Patent No. 5,728,379) and Yamamura (Cancer Res 5/2001, 61: 3969-3977), and under under 35 U.S.C. 103(a) as being unpatentable over Yamamura (Cancer Res 5/2001, 61: 3969-3977) and Chung et al. (J Virol, 1999, 73: 7556-7564) are moot since Applicant cancelled the claim in the response filed on 03/23/2007.

The rejections of claim 19 under 35 U.S.C. 103(a) as being unpatentable over Chung et al., in view of Yamamura et al. and Chung et al. taken with Yamamura et al.,

in further view of Tjuvajev et al. (Cancer Res, 1998, 58: 4333-4341, Abstract) are moot since Applicant cancelled the claim in the response filed on 03/23/2007.

The rejection of claims 10-13 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in response to Applicant's amendment to the claims filed on 03/19/2007.

The rejection of claim 34 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps is withdrawn in response to Applicant's amendment to the claim filed on 03/19/2007.

The rejection of claims 29-36 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps is withdrawn in response to Applicant's amendment to the claim filed on 03/19/2007. However, in response to Applicant's amendments to the claims, new grounds of rejections are made below.

The rejection of claims 1, 3-18, 20-22, and 25-28 are under 35 U.S.C. 103(a) as being unpatentable over Van Meir et al. (PGPUB 2005/0074430), in view of both LaFace (U.S. Patent No. 6,649,158) and Yamamura et al. is withdrawn in response to Applicant's amendments to the claims filed on 03/19/2007.

The rejection of claims 26-34 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in response to Applicant's amendment to the claim filed on 03/19/2007.

Specification

4. The specification is objected to for the reasons of record set forth in the non-final Office Action of 04/21/2006. However, upon Applicants request, the submission of a re-translated version of the specification is deferred.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1 and 3, 4, 6, and 7 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 10/477,797 in view of Martuza (U.S. Patent No. 5,728,379, of record) and Yamamura (Cancer Res 5/2001, 61: 3969-3977, of record). Although the

conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant has requested that the obvious-type double patenting rejections set forth by the Examiner be held in abeyance. The Applicants' comments are acknowledged, however the rejection will be maintained until a Terminal Disclaimer is filed or claims are amended to obviate the rejection.

Claim Rejections - 35 USC § 112, 2nd paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

8. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps disclosing how the suppression of viral expression/replication is achieved.

9. Claims 29 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point

Claim 29, reciting a therapeutic method for suppressing fibrosis and malignant tumors by replicating an HSV vector to selectively disrupt the proliferation of myofibroblast by expressing a protein that promotes apoptosis, is unclear. It is not

clear, from the language of the claims, how inhibition of myofibroblast proliferation and expression of a pro-apoptotic factor in myofibroblasts leads to inhibition of apoptosis in malignant tumors. The metes and bounds of the claim cannot be determined and the claim is indefinite.

Claim 30 is rejected for being dependent from the rejected claim 29 and also for failing to further clarify the basis of the rejection.

Claim Rejections - 35 USC § 112 - enablement

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1, 3, 4, 6-13, 18, and 20-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an HSV vector comprising SEQ ID NO: 3 operably linked to an ICP4 gene and a TK gene, does not reasonably provide enablement for any other vector comprising SEQ ID NO: 1 or SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

Applicant argues that the activity of the calponin promoter is strongest in the region from -260 to + 73 and it is rapidly reduced in the region from -219 to +73 as shown in Fig. 1A in Yamamura et al. (Cancer Res, 2001, 61: 3969-3977) and therefore the calponin promoter is recognized as the region encompassing the 41 nucleotides located between positions -260 and -219. Applicant submits that one of skill in the art would understand how to make and use the invention commensurate with the scope of the claims and requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however the rejection is maintained for the reasons of record set forth in the prior Office actions. Specifically, Applicant claims a vector that is capable of cell-specific expression. Although Yamamura et al. teach that the sequence between positions -260 and -219 is essential for inducing calponin gene transcription in HOS (osteosarcoma) and HMC (mesangial) cell lines, they do not teach that this region can by itself promote tissue specificity. There is a difference between induction of transcription and tissue/cell specificity. Absent evidence to the contrary, the sequence between positions -260 and -219 can perform equally well in

different tissues/cells (i.e., does not confer cell specificity) and it is possible that additional regions of the calponin promoter, other than positions -260 and –219, are required to confer tissue/cell specificity. Yamamura et al. teach that the sequence between positions -260 and -219 includes consensus-binding sites for Sox and GATA-1 transcription factors. However, these factors can control transcription from a variety of promoters in different cell and tissue types. Yamamura et al. do not teach that they are indeed implicated in conferring tissue/cell specificity for the calponin promoter. The question is not whether one of skill in the art would know how to make a vector comprising the promoter set forth by SEQ ID NO: 1; the question is whether such a vector would work according to the claims, i.e., driving cell-specific expression. The art does not teach, and Applicant did not demonstrate, that SEQ ID NOs: 1 by itself (i.e., only positions -260 and -219 of the calponin promoter) is sufficient to confer tissue/cell specificity (a feature essential for the claimed invention); the art and the specification only teach SEQ ID NO: 3 (i.e., the full length promoter) as having tissue specificity. Therefore, one of skill in the art would readily understand that other regions other than of the positions -260 and -219 are important for promoting cell specific activity. For these reasons, the rejection is maintained.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1, 3, 6, and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza (U.S. Patent No. 5,728,379, of record), in view of both Yamamura (Cancer Res 5/2001, 61: 3969-3977, of record) and Chung et al. (J Virol, 1999, 73: 7556-7564, of record), for the reasons of record set forth in the prior Office actions.

* Since the claims are enabled for an HSV vector comprising the tissue/cell specific promoter set forth by SEQ ID NO.: 3 (see above), the instant rejection is applied to the extent that the claims read on SEQ ID NO.: 3, which comprises SEQ ID NO.: 1 and SEQ ID NO.: 2.

Applicant argues that Martuza uses a different method of making the oncolytic virus as compared to the method disclosed in the instant specification, which is more efficient and more rapid than the previously known method. Specifically, Applicant points out that the disclosed method uses homologous recombination at the ribonucleotide reductase gene locus, which was not known and was not an obvious method to use at the time the invention was made. Applicant argues that Martuza discloses using this method years after the filing of the '379 patent (i.e., 2005) and concludes that Martuza was not able to use this technique until 2005 and that one of skill in the art would not have found it obvious to even combine the teachings of Martuza and Yamamura. Applicant continues arguing that one of skill in the art would not have been expected to have a reasonable expectation of success in making such a virus because any one of *lacZ*, cell specific promoter, and ICP4 gene may ablate during

homologous recombination at the ribonucleotide reductase gene locus or because of the difficulty of cloning a vector even when such a vector with the appropriate recombination locus has been produced.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

First, it is noted that the instant claims are drawn to a composition, and not to a method of obtaining the composition and that the patentability of the composition does not depend on the method of obtaining it (see MPEP 2113 [R-1]). The fact of the matter is that the instant end product (i.e., the instant HSV vector) is identical to the end product taught by the combined teachings above. Applicant did not provide any evidence that the HSV vector taught by the combined cited references is structurally different from the instant HSV vector. Additionally, beside arguments, Applicant did not provide any evidence that one of skill in the art would not have been expected to have a reasonable expectation of success in making such a vector. Second, Applicant's argument that homologous recombination at the ribonucleotide reductase gene locus was unknown that one of skill in the art would not have been motivated or expected to have a reasonable expectation of success in using it is not found persuasive because the prior art teaches the successful use of homologous recombination in general, including homologous recombination at the ribonucleotide reductase gene locus. For instance, Chung et al. teach using homologous recombination to obtain an HSV vector comprising the B-myb promoter-γ34.5 sequence inserted in the ribonucleotide reductase locus (claim 19) (p. 7558, Fig. 1, p. 7557, column 1, second paragraph and column 2,

Results). Therefore, the claimed invention was *prima facie* obvious at the time the invention was made.

14. Claims 1, 3, 4, 6, 7, 14, 16-18, 20, and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chung et al., in view of Yamamura et al. for the reasons of record set forth in the final Office action.

* Since the claims are enabled for an HSV vector comprising the tissue/cell specific promoter set forth by SEQ ID NO.: 3 (see above), the instant rejection is applied to the extent that the claims read on SEQ ID NO.: 3, which comprises SEQ ID NO.: 1 and SEQ ID NO.: 2.

Applicant argues that, since both Chung et al. and Yamamura et al. use only one promoter to drive the expression of γ34.5 and ICP4 gene, both references teach away from using multiple promoters. Applicant continues arguing that both references teach that the vectors should be tightly regulated to effectively target cancer cells. Applicant submits that, since the instant invention uses two promoters, the calponin promoter and the ICP4 promoter in order to achieve a HSV vector that target proliferating smooth muscle cell, the combination of Chung et al. and Yamamura et al. does not teach or suggest the instant invention.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

The combined teachings of Chung et al. and Yamamura et al. disclose an HSV vector comprising the calponin promoter driving the expression of the γ34.5, wherein the

ICP4 gene is intact, i.e., the vector encodes ICP4 (i.e., a transcription factor essential for viral replication) integrated downstream to the ICP4 transcriptional initiation regulatory region. Therefore, the vector of Chung et al. and Yamamura et al. uses two promoters and Applicant's arguments are not found persuasive. The rejection is maintained.

15. Claims 1, 3, 4, 6, 7, 14, 16-18, 20, and 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chung et al. taken with Yamamura et al., as applied to claims 3-7, 14, 16-20, and 25-28 above, in further view of Tjuvajev et al. (Cancer Res, 1998, 58: 4333-4341, Abstract; of record) for the reasons of record set forth in the final Office action.

Applicant's arguments are the same as above. The rejection is maintained for the reasons stated above.

New Rejections/Objections

Claim Objections

16. Claim 29 is objected to because of the following informalities: the claim recites "promote apoptosis". Appropriate correction to "promotes apoptosis" is required.

17. Claim 27 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper

dependent form, or rewrite the claim(s) in independent form. Specifically, claim 26, from which claim 27 depends, recites that proliferating smooth muscle cells are targeted, while claim 26 recites broader range of targeted cells.

Claim Rejections - 35 USC § 112, 2nd paragraph

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

19. Claims 35 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35 is presented in such a language that the scope of the claims is difficult to ascertain. To enumerate a few examples, it is not clear how a solution comprising a cell can be inserted into a gene fragment or what the gene fragment is. Since the metes and bounds of the claims cannot be determined, the claim is indefinite.

Claim 36 is rejected for being dependent from the rejected claim 35 and also for failing to further clarify the basis of the rejection.

20. Claims 29-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29-34 recite the limitation an HSV vector of claim 1 expressing a gene, protein or peptide, wherein the gene, protein or peptide can promote apoptosis (claims 29 and 30). There is insufficient antecedent basis for these limitations in the claims.

Additionally, claims 31-34, reciting a therapeutic method for suppressing proliferating vascular lesions or glomerulonephritis by replicating an HSV vector that expresses a gene, protein, or peptide, are unclear. There is no nexus between the expression of a gene, protein, or peptide and suppression of proliferation.

21. Claims 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Since the art does not teach more than one human calponin gene, it is not clear what Applicant means by the recitation of "a human calponin gene" in claim 6. The metes and bounds of the claim cannot be determined and the claim is indefinite.

Claim 7 is rejected for being dependent from the rejected claim 6 and also for failing to further clarify the basis of the rejection.

22. Claims 1, 3, 4, 6-13, 18, and 20-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not clear what Applicant means by "infecting a virus mixed solution of the homologous recombination to a cell", as recited in claim 1. Additionally, claim 1 recites

"a ribonucleotide reductase locus". Since the art does not teach more than one ribonucleotide reductase locus, it is not clear what Applicant means by this recitation. The metes and bounds of the claim cannot be determined and the claim is indefinite.

Claims 3, 4, 6-13, 18, and 20-34 are rejected for being dependent from the rejected claim 1 and also for failing to further clarify the basis of the rejection.

23. Claims 31-34 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. Specifically, there is no nexus between expressing a gene, protein, or a peptide and suppressing cell proliferation.

Claim Rejections - 35 USC § 112, new matter

24. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

25. Claims 1, 3, 4, 6-13, 18, and 20-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

It is noted that the original claims recited a vector that does not replicate in "adult normal cells". In the response filed on 07/21/2006, Applicant amended the claims to recite a vector that "is not expressed or replicated in normal differentiated cells". Upon further consideration, the amendment to recite "not expressed or replicated in normal differentiated cells" is considered new matter because there is no support in the specification for specifically selecting normal differentiated cells. The specification only provides support for a vector that does not replicate in "normal adult cells". It is noted that the genus of "adult normal cells" is broad and encompasses normal differentiated and undifferentiated cells (such as stem cells) found in the adult organism. The specification does not provide any basis for excluding cells such as the normal stem cells mentioned above.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often

necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

26. Claims 1, 3, 4, 6-13, 18, and 20-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Specifically, the amendment to the claims to include a "gene encoding a transcription factor essential for initiation of a herpes vial replication which is integrated downstream of the transcriptional initiation regulatory region of an ICP4 gene" (claims 1 and 35), a desired protein expressed "under the control of said transcriptional initiation regulatory region of the ICP4 gene" (claims 8 and 9), or " is considered new matter. It is noted that claims 3, 4, 6, 7, 18, 20-34 are directly or indirectly dependent from claims 1, that claims 9-13 are directly or indirectly dependent from claims 8 and 9, and that claim 36 is dependent from claim 35; therefore these claims all include the embodiments that represent new matter.

The original claims and the specification fail to provide support for these recitations. The original claims clearly recited that a cell-specific transcriptional initiation regulatory region, wherein the cell-specific transcriptional initiation regulatory region is

the calponin promoter, drives the expression of a predetermined gene, wherein the predetermined gene encodes a viral replication gene such as ICP4, i.e., a transcription factor (see claim listings of 06/24/2004 and 07/21/2006). The specification clearly discloses only the embodiment wherein the predetermined gene is a transcription factor, whose expression is driven by the calponin promoter; there is no support for the embodiment of the ICP4 gene promoter driving the expression of the transcription factor (see p. 4, paragraph 0019, p. 5, paragraph 0022 and Fig 1, p. 6, paragraphs 0031, 0034, and 0035). With respect to the desired protein, the specification only discloses that the desired protein is under the control of the calponin promoter (p. 6, paragraph 0035).

In addition to the above, the amendment to claim 35 to recite inserting the solution comprising a cell of step (a) into a gene fragment (step (b)) introduced new matter, because the specification does not provide any support for such an embodiment. Claim 36 is dependent from claim 35 and therefore includes the embodiment that represents new matter.

Claim Rejections - 35 USC § 112, enablement

27. Claims 1, 3, 4, 6-13, 18, and 20-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Factors to be considered in determining whether a

disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

As amended, the claims are drawn to an HSV vector comprising the calponin promoter, a gene encoding a transcription factor essential for HSV replication integrated downstream of the ICP4 promoter, and thymidine kinase. The claims require the vector not to be expressed or replicated in normal differentiated cells. While the calponin promoter is specific for proliferating cells overexpressing calponin, such as proliferating smooth muscle cells and some tumor cells, the claim does not require calponin promoter to drive the expression of transcription factor essential for HSV replication. In fact, the claims require the transcription factor to be expressed from the ICP4 gene promoter. It is noted that, since the ICP4 promoter is not cell-specific, the transcription factor controlling replication and expression of the HSV vector would be expressed in normal differentiated cells, which in turn would initiate replication and expression of the HSV vector in normal differentiated cells, embodiment excluded by the claims. Neither

the art nor the specification teaches that such a vector would not proliferate in normal differentiated cells. Therefore, one of skill in the art would readily recognized that, although it could be obtained, such a vector would not have the claimed properties (i.e., not to be replicated and expressed in normal differentiated cells) (claims 1, 3, 4, 6-13, 18), properties essential for the claimed invention. With respect to the claimed therapeutic method, it is noted that the art teaches that successful therapy is dependent on tissue or cell-specific targeting of the therapeutic vectors, wherein such targeting avoids toxicity to normal differentiated cells (see Hardcastle et al., Current Cancer Drug Targets, 2007, 7: 181-189, p. 181, column 1, p. 182, column 1; Miyatake, Human Cell, 2002, 15: 130-137, Abstract, p. 130 bridging p. 131, p. 134, column 1). The claimed vector has no such specificity, since no transcription factor required for HSV replication is under the control of the calponin promoter, i.e., conditionally expressed. For these reasons, one of skill in the art would also recognize that such a vector cannot be used as claimed, i.e., to specifically express or suppress a gene in cells other that normal differentiated cells (claims 20-25) and to specifically treat fibrosis, malignant tumors, proliferating vascular lesions or proliferating glomerulonephritis (claims 26-34).

With respect to claims 35 and 36, neither the art nor the specification teaches that a solution comprising a cell can be inserted into a gene fragment (compare steps (a) and (b) in claim 35). One of skill in the art would readily recognize that such an embodiment is impossible to be achieved, since a cell (or even a solution) cannot be inserted into a gene.

In conclusion, the claimed invention is not enabled by the specification or the art.

Claim Rejections - 35 USC § 103

28. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

29. Claims 1, 3, 4, 6, 7, 18, 20-22, and 25-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chung et al., in view of each Yamamura et al., Van Meir et al. (PGPUB 2005/0074430, of record), and Miyatake et al. (Stroke, 1999, 30: 2431-2439).

* Since the claims are enabled for an HSV vector comprising the tissue/cell specific promoter set forth by SEQ ID NO.: 3 (see above), the instant rejection is applied to the extent that the claims read on SEQ ID NO.: 3, which comprises SEQ ID NO.: 1 and SEQ ID NO.: 2.

Chung et al. teach an HSV vector comprising the cell cycle regulated B-myb promoter integrated upstream of the predetermined viral gene γ34.5 (i.e., a viral replication-related gene, essential for viral replication) and an intact thymidine kinase (tk) gene, wherein the HSV vector does not replicate in the normal, differentiated cells (claims 1, 3, 4, 14, 16, and 17) (Abstract, p. 7556, column 2, last paragraph, p. 7558, Fig. 1, p. 7561, column 2, p. 7563, column 1), wherein the vector comprises a deletion of the gene encoding the viral ribonucleotide reductase and wherein the B-myb promoter-γ34.5 sequence is inserted in the ribonucleotide reductase locus (claim 1) (p. 7558, Fig. 1, p. 7557, column 1, second paragraph and column 2, *Results*). Chung et al. teach that the vector is specific for cycling cells, i.e., the vector is specific for

proliferating cells, such as tumor (claim 18) (p. 7556, column 2, second paragraph, p. 7562, column 2, last paragraph) and that the vector has *in vivo* anticancer effects when tested in a mouse model, i.e., Chung et al. teach a method for the expression/replication of the vector encoding for the replication-related gene (claim 20) (p. 7560, column 2). Since the vector of Chung et al. has an intact ICP4 gene, the vector encodes ICP4 (i.e., a transcription factor essential for viral replication) integrated downstream to the ICP4 transcriptional initiation regulatory region (claim 1). Chung et al. do not teach the calponin promoter as set forth in SEQ ID No.: 3 or the 4F2 enhancer (claims 6 and 7), nor do they teach a method of suppressing the expression of a gene expressed by the HSV buy using acyclovir or ganciclovir (claims 21 and 22). Yamamura et al. teach a replication competent HSV vector comprising the calponin promoter as set forth in SEQ ID NO.: 3 and the 4F2 enhancer upstream of it, wherein the vector inhibits the growth of human soft and bone tumor growth in experimental animals (claims 1, 3, 4, 6, 7, 25, 27, and 28) (Abstract, p. 3969, column 1, p. 3972, column 1, p. 3973, columns 1 and 2, p. 3974, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the vector of Chung et al. by replacing the B-myb promoter with the calponin promoter/4F2 enhancer of Yamamura et al., with a reasonable expectation of success. The motivation to replace the B-myb promoter with the calponin promoter is provided by Yamamoto et al., who teach that calponin is aberrantly expressed in a wide variety of human soft tissue and bone tumors and therefore, the calponin promoter could be used to target therapeutics to the human practically any soft or bone tumor cell (Abstract, p. 3969, column 2, p. 3976, column 1).

The motivation to use the 4F2 enhancer is also provided by Yamamoto et al., who teach that insertion of the 4F2 enhancer upstream of the calponin promoter increases the transcriptional activity of the promoter (p. 3972, column 1). One of skill in the art would have been expected to have a reasonable expectation of success in making such a vector because the art teaches that such vectors can be successfully made.

Chung et al. taken with Yamamura et al. do not teach a method of suppressing the expression of a gene expressed by the HSV buy using acyclovir or ganciclovir (claims 21 and 22). Van Meir et al. teach adenoviral or HSV vectors that selectively replicate into hypoxic tumor cells, wherein the vector comprises hypoxia-responsive elements operably linked to a promoter integrated upstream of a gene encoding for a protein that modulates viral replication, such as E1A, and an intact *tk* gene that allows for the termination of viral propagation with an exogenous agents such as ganciclovir (claims 21, 22, and 34) (Abstract, p.1, paragraph 003, p.3, paragraph 0020, p. 7, paragraphs 0071 and 0074, p. 7, paragraph 0069). Van Meir et al. also teach that the vectors have *in vivo* anticancer effects when tested in a mouse model, i.e., Van Meir et al. teach a method for the expression/replication of the vector encoding for the replication-related gene (claim 20) (Example 15). It would have been obvious to one of skill in the art, at the time the invention was made, to terminate the propagation of the vector taught by Chung et al. and Yamamura et al. by using ganciclovir, as taught by Van Meir et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to terminate viral propagation when needed. One of skill in the art would have been expected to have a reasonable expectation of

success in doing such because the art teaches that ganciclovir can be successfully used to terminate rfeplication of HSV vectors comprising an intact *tk*. With respect to the limitations of therapy by targeting the virus to proliferating smooth muscle cells (claims 26, 29-31) or of therapy for glomerulonephritis (claim 32), these are not innovative over the prior art. For example, the art teaches using HSV vectors to inhibit smooth muscle cell proliferation (see Miyatake et al., the whole paper). One of skill in the art would have known, would have been motivated, and would have been expected to have a reasonable expectation of success in using the vector taught by Chung et al., Yamamura et al., and Van Meir et al. to treat proliferative disorders such as glomerulonephritis and disorders associated with smooth muscle cell proliferation, because the art teaches the usefulness of using such vectors to treat these disorders. Similarly, the limitation of systemic administration (claim 33) is not innovative over the prior art, such route was routinely used before the invention was made.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

30. It is noted that the art rejection are not inconsistent with the enablement rejection because the cited art teaches HSV vectors wherein the ICP4 gene is intact (i.e., the ICP4 transcription factor essential for viral replication is downstream of the ICP4 promoter) and, since the calponin promoter drives the expression of transcription factors essential for HSV replication such as ICP4 (Martuza et al.) or γ34.5 (Chung et al.), the vectors are conditionally replicating vectors (i.e., they replicate only in cells

overexpressing calponin, such as proliferating smooth muscle cells and malignant cells). By contrast, the vectors recited in the instant claim do not disclose that calponin promoter drives the expression of a transcription factor essential for HSV replication, hence the enablement rejection. The term "comprising" in the instant claims is open-ended and does not exclude additional elements, i.e., a transcription factor downstream of the calponin promoter. Therefore, the vectors taught by the above cited art meet all the claim limitations.

31. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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